ORIGINAL PAPER

Transtympanic steroids in refractory sudden hearing loss. Personal experience

Terapia steroidea transtimpanica nell'ipoacusia improvvisa refrattaria. Nostra esperienza

I. DALLAN, L. BRUSCHINI, A. NACCI[1], B. FATTORI[1], A.C. TRAINO[2], F. ROGNINI, G. FERRARO, P. BRUSCHINI
2nd ENT Unit, Azienda Ospedaliera Universitaria Pisana; [1] Department of Neurosciences, 3rd ENT Unit, University of Pisa; [2] U.O. Health Physics, Medical Physics Section, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy

Key words

Sensorineural hearing loss • Sudden hearing loss • Transtympanic therapy • Steroids

Parole chiave

Ipoacusia neurosensoriale • Ipoacusia improvvisa • Terapia transtimpanica • Steroidi

Summary

The treatment of choice for sudden sensorineural hearing loss is still lacking. Many drugs have been used over the years, with varying results and steroids have proven to be effective in clinical trials, albeit systemic administration is associated with untoward side-effects and cannot be used in all patients. The transtympanic approach presents two main advantages: first, it allows higher concentrations in the inner ear environment and, second, it minimizes systemic absorption. Aim of the present investigation was to establish the effectiveness of transtympanic steroid treatment for sudden sensorineural hearing loss in patients in whom conventional treatment had failed. For this purpose, a prospective, non-randomized study was designed to evaluate hearing improvement in sudden sensorineural hearing loss patients treated with transtympanic steroids. A solution of methyl-prednisolone and sodium bicarbonate was administered, via a transtympanic injection, in 10 patients. Hearing levels were evaluated before treatment and on days 1, 7 and 30, thereafter. Improvement in hearing was observed in 70% of patients, moreover, in patients not usually considered amenable to this kind of treatment. Transtympanic steroid treatment is an effective and safe option for patients with sudden sensorineural hearing loss when conventional treatment regimens have failed. Further studies are needed to define the optimal dosage, route of administration and type of steroids.

Riassunto

La terapia ottimale dell'ipoacusia improvvisa non è stata ancora definita. Molti farmaci sono stati utilizzati con diversi risultati ma gli steroidi hanno dimostrato la loro efficacia in trial clinici. Sfortunatamente essi presentano numerosi effetti collaterali e non possono essere utilizzati in tutti i pazienti. La via transtimpanica offre due grandi vantaggi: permette di ottenere concentrazioni elevate di farmaco a livello dell'orecchio interno e di ridurre al minimo l'assorbimento sistemico. Partendo da questi presupposti abbiamo impostato uno studio prospettico non randomizzato per valutare l'efficacia del trattamento steroideo transtimpanico nei pazienti con ipoacusia improvvisa che non avevano risposto alla terapia tradizionale (cortisonici ed emoreologici e.v.). Una soluzione di metil-prednisolone e bicarbonato di sodio è stata iniettata nell'orecchio medio in 10 pazienti. La valutazione audiologica è stata eseguita prima del trattamento e ai giorni 1, 7 e 30 dopo il trattamento. Un miglioramento uditivo è stato ottenuto nel 70% dei pazienti. Per di più questi pazienti sono considerati spesso fuori dalle possibilità terapeutiche. La terapia transtimpanica con steroidi si è dimostrata efficace nei pazienti con ipoacusia improvvisa che non avevano risposto alla terapia tradizionale. Ulteriori studi sono necessari per definire con esattezza il tipo di steroide, il miglior dosaggio e la via di somministrazione ottimale.

Introduction

Sudden sensorineural hearing loss (SSHL) is one of the causes of otologic emergencies. It is defined as > 20 dB of hearing loss over at least 3 contiguous frequencies occurring within 3 days [1 2]. Aetiologically, many causes, such as viral cochleitis, vascular injury, autoimmune inflammation and inner ear membrane rupture have been proposed [3]. Viral and vascular aetiologies are the most convincing.

The natural history of SSHL is unknown; spontaneous recovery occurs in approximately 30% of cases [4] and recovery occurs mainly within the first 2 weeks after onset. Many factors appear to affect recovery; the degree of hearing loss, the shape of the audiogram, the presence of vertigo and the time between the onset of SSHL and therapy probably being the most important.

Low and mid frequency hearing loss recover more frequently than flat or high frequency loss [5 6]. The more severe the hearing loss, the more difficult the recovery. From a therapeutic point of view, many drugs have been used with variable results [1]; "shotgun" therapy (many drugs associated together) is one

of the most common choices but there is no clear evidence that it offers better outcome than spontaneous recovery [1].

Steroids have been demonstrated to be effective [1] even if further results are needed. Prompt administration of systemic steroids have been shown to increase the rate of hearing recovery [4]. It should be stressed that high doses of steroids can be associated with systemic effects and cannot be used in all patients.

The transtympanic route presents two main advantages: i) it is possible to obtain a higher concentration of the drug in the inner ear and, ii) it is possible to reduce the side-effects due to systemic absorption.

Effectiveness of local application of steroids in SSHL has been reported by many Authors [2 6-8]. Steroids have been used also in Ménière's disease [9 10] and in other inner ear conditions [11]. Optimal dosage, drug and route of administration still remain a matter of debate.

Corticosteroids have multiple mechanisms of action including immune suppression, anti-inflammatory action, membrane stabilization, ion balance regulation and increased perfusion [12]. Steroids have been shown to be effective also when no immune disorders can be demonstrated [13].

Based on these considerations, we started treating SSHL patients, not responding to traditional therapy, with transtympanic steroids in order to better understand the real effectiveness of this treatment.

Patients and methods

Enrolled in the study were 12 consecutive patients, 7 females and 5 males, admitted to our Department from July 2003 to July 2004 and affected by SSHL not responsing to traditional treatment. This group represents 44% of the SSHL patients hospitalised in our institution in the same period. All patients were informed about their condition and the treatment options. All patients gave their consent to the treatment and all took part in the study protocol (Table I). In 5 patients, vestibular evoked myogenic potentials (VEMPs) and speech discrimination tests were also performed. All patients, except 2, completed a follow-up of at least 6 months. These 2 patients were not included in the statistical analyses.

Pure-tone audiometry (PTA), performed before transtympanic treatment, showed a severe to profound hearing loss in 8 patients and a moderate hearing loss in the other two. Overall, mean PTA was 84.9 ± 20.9 SD dB.

Mean age of the patients was 54 ± 20 SD years (range 28-81). The mean interval between the onset of SSHL and transtympanic therapy was 33.3 ± 45.1 SD days (range 11-159). Eleven patients received a single injection, one received three. Middle ear disease was ruled out in all patients.

All patients were admitted and treated with a steroid i.v., namely, Methyl-Prednisolone, (MP) (1 mg/kg/die), and with a pentoxifilline i.v. (200 mg/die). In 3 patients, low molecular weight heparins (0.4 ml s.c. b.i.d.) were also given.

If the patient showed no improvement with the systemic therapy after 10 days of treatment, transtympanic steroids were given. One ml of MP 40 mg/ml was buffered with 1 ml of sodium bicarbonate in order to obtain a less acid solution. After local anaesthesia, a transtympanic injection, usually in the round window (RW) area, was performed and approximately 0.5-1 ml of the solution was placed in the middle ear. The patient was then invited not to swallow and to remain with his/her head turned to the opposite side for 20-30 minutes. Antibiotic therapy was given to all patients for 3 days.

A change ≥ 15 dB in mean pure tone (PTA, 4 frequencies 0.5, 1, 2, 3 kHz) was considered significant.

Table I. Study protocol in SSHL patients.

Study protocol
o Otoscopy
o Blood test*
o Audiometry (PTA†)
o Tympanometry
o Stapedius reflex
o Vestibular examination (bithermal caloric test)
o Ultrasound studies (duplex scanning and Doppler) of neck vessels
o CT scan (head plus iodine contrast and temporal bone with bone algorithm)

* including markers of vascular risk (Lipoprotein A, Apolipoprotein A, Apolipotrotein B, D-dimer, AT III)
† Mean pure-tone at 4 frequencies (0.5, 1, 2, 3 kHz)

Table II. Audiological results.

Patient	Sex	Side	Age (yrs)	Time between SSHL and transtympanic treatment (days)	PTA before CTT	PTA day 1	PTA day 7	PTA day 30	Δ PTA	N. injections
N.E.	F	R	73	15	75	60	45	30	45	1
G.A.	M	R	70	39	120	65	65	70	50	1
S.E.	M	L	61	19	85	62	62	62	23	1
M.F.	M	R	60	11	80	60	45	45	35	1
C.P.	F	L	70	29	68	70	55	36	32	1
M.L.	F	L	81	11	120	115	112	112	8	1
F.I.	F	L	34	159	75	70	90	92	-17	1
G.P.	F	L	28	15	90	90	85	63	27	1
DB.F.	M	R	32	11	54	54	38	38	16	1
M.D.	F	R	36	24	82	77	35	77	5	3

R: right L: left

Statistical methods

A t test for paired data was used to compare the b-PTA data with those of PTA-1, PTA-7 and PTA-30.

Results

Mean PTA before transtympanic treatment was 84.9 ± 20.9 SD dB; at day 30, after local steroid administration, mean PTA was 62.5 ± 26.3 SD dB.

PTA improvement was documented in 9 patients after local administration of MP; in 7 of these, improvement was significant. These data are outlined in Table II.

The relationships between PTA values, before and during follow-up (before treatment and 1, 7 and 30 days after treatment) for all patients is plotted in Figure 1.

The statistical results, obtained with t test for paired data, indicate:

1) The time course (before treatment (b-PTA) and at days 1, 7 and 30 after treatment) of PTA levels, estimated by the t test, shows a significant trend ($p < 0.05$);
2) Comparing b-PTA with PTA-1 and PTA-7, a statistically significant difference was found between b-PTA and PTA-7 ($p < 0.05$). No statistically significant difference was observed between b-PTA and PTA-1. These data (mean values and p values) are summarized in Table III;
3) No correlation was found between PTA improvement (ΔPTA) and age, nor between the time to the transtympanic treatment and PTA improvement (ΔPTA). In our opinion, these results are also probably due to the small number of patients.

The computed tomography (CT) scan was normal in 8 subjects (in 2 of whom a carotid calcification was observed at the level of the cavernous sinus). One patient presented an atrophic area in the left temporal bone, due to concussion which had occurred 10 years previously. Another patient presented signs of neurovascular disease.

Vestibular examination was normal in 5 patients. Four patients had a vestibular paresis which was not compensated in two of them. Another patient had hyperreflexia. Five patients underwent a VEMPs examination. In two cases, the sacculo-collic reflex was absent on the same side as the hearing loss. VEMPs were normal in the other three patients.

In 8 patients, blood examination revealed a mild vascular risk (6 patients with elevated levels of cholesterol and 5 patients with alterations of apolipoprotein and lipoprotein A plasma levels; in 3 patients, multiple alterations were observed together).

Nine patients underwent ultrasound studies (duplex scanning and Doppler) of the neck vessels; the examination was normal in 6 patients. In three, a mild thickening of the carotid walls was observed.

Table III. Mean value and SD before and after transtympanic therapy.

Variable	Mean ± SD	Statistical results (p)		
PTA-b	85 ± 21			
PTA-1	72 ± 18	n.s.		
PTA-7	63 ± 25		< 0.05	
PTA-30	63 ± 26			< 0.05

PTA-b: PTA before transtympanic therapy
PTA-1 (7,30): PTA at day 1 (7,30) after transtympanic therapy
SD: standard deviation
n.s.: not significant

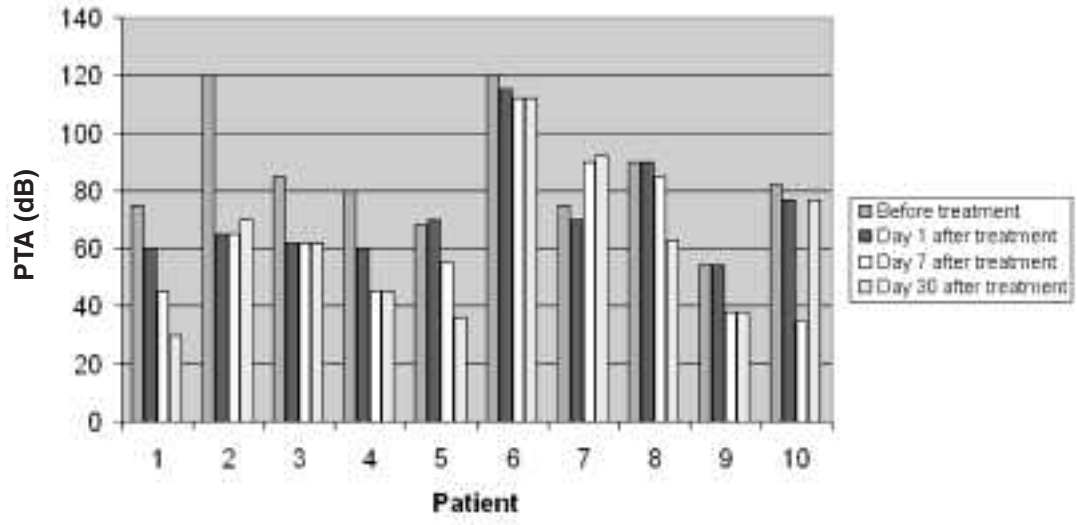

Fig. 1. Individual PTA for patients receiving transtympanic methyl-prednisolone.

No patient suffered any complications from the transtympanic application of MP.

Discussion

SSHL is not a disease per se; it has to be considered as a manifestation of an underlying pathology. Thus it can be considered as a diagnosis of exclusion. The incidence of SSHL is estimated in 5 to 20 per 100000 every year [5]. Hearing loss is associated with many molecular, biochemical and physiologic changes such as DNA damage, reduction in mitochondrial function, reduced water concentration, ionic changes and reduced elasticity of the cellular membrane [14]. The role of reactive oxygen species (ROS) has proved important in the pathogenesis of sudden hearing loss. Antioxidants have been used both systematically [15] and transtympanically [16]. Despite different noxae (viral or vascular), the final damage-pathway might be the same. Moreover, an immunologically mediated vasculitis, with a consequent cochlear hypoperfusion, has been experimentally demonstrated [17]. The role of endothelial cells in this mechanism is pointed out; these cells may promote vasculitis by secreting cytochines [17].

Many drugs have been used in SSHL treatment and steroids have been demonstrated effective in clinical trials [4]. Despite recognized clinical efficacy, the real mechanism of action of steroids on cochlear function is still unknown. Traditionally, their effect has been attributed to the anti-inflammatory and immunosuppressive activity of these drugs; neuroprotective, antioxidant and antiapoptotic effects have also been reported [18-20]. Furthermore, glucocorticoid and mineralocorticoid receptors have been demonstrated in the inner ear [13]. In this way, steroids can modulate gene expression. Moreover, they seem to be able to control the immunologically mediated vasculitis by inhibiting cytochine secretion [17]; in fact, they have also been shown to act not only on hair cells but also on cochlear vessels [17].

Aquaporins (AQP) have been demonstrated in the inner ear [21]. These molecules are involved in a homeostatic mechanism in the inner ear regarding water and ion balance [22]. Transtympanic steroids have been demonstrated to up-regulate AQP1 mRNA in a dose-dependent manner [23]. It is possible that local administration of steroids can modulate the inner ear environment, via the AQP1 pathway, thus balancing inner ear fluids. Moreover, they have proven to increase Na^+-K^+ exchange in the stria vascularis, thus restoring normal endolymph ion balance [13] and consequently endocochlear potential [13]. Furthermore, steroids have proven to restore stria vascularis morphology, maybe by restoring ion balances [24].

Systemic administration of these drugs is often complicated with troublesome side-effects and not all patients can be treated with steroids. The inner ear is isolated physically and anatomically from the remaining part of the body by a labyrinth-blood barrier [25] and so the possibility of delivering drugs directly to the inner ear allows a more target-specific treatment [14]. The transtympanic route has 2 advantages; firstly, it allows a greater concentration of drugs in the perilymph and, secondly, it minimizes systemic

effects and absorption. Local administration of steroids has been used with good results [2 6-8].

MP presents a better absorption profile after transtympanic administration than hydrocortisone and dexamethasone [11]. Steroids are taken into the inner ear via RW [11]; many factors seem to affect the passage of the substances through the RW into the inner ear. A detailed review has been produced recently by Banerjee and Parnes [26]. Local steroid administration is safe; no morphologic or functional alterations in the ear have been demonstrated in experimental animals after transtympanic application [27].

In this study, we administered MP, via a transtympanic route, in patients with SSHL in whom a conventional therapy had failed. A significant response (defined as PTA improvement ≥ 15 dB) was obtained in 7 of the 10 patients.

We found no correlation between vestibular involvement and poor outcome; two of the three unsuccessful cses presented a normal vestibular function (evaluated with caloric testing). Although this observation is in contrast with those in the medical Literature, our data are, in our opinion, too limited to be significant. The only patient with vestibular paresis and saccular dysfunction (evaluated with VEMPs) presented no improvement. Theoretically, VEMPs have a more prognostic value than caloric testing because they investigate the sacculus, which is closer to the cochlea than to the lateral semicircular canal. Moreover, our results suggest that the PTA improvement does not depend on the basal PTA levels. As far as concerns this observation, it must be borne in mind that our statistical results refer to a small group of patients and they need to be confirmed with a larger number of patients.

Moreover, we observed 3 patients that almost recovered their previous hearing level (estimated on the opposite side). For those who did not achieve complete recovery, earlier transtympanic therapy might have obtained a better outcome. Overall, the average PTA improvement was 22.4 ± 20.1 SD dB.

In contrast with our previous evaluation, statistical evaluation seems to confirm that the main hearing improvement occurs during the first seven days after transtympanic therapy. However, we have noted that hearing improvement may be seen even 10 days after steroid administration. This is probably due to various causes including inner ear environment improvement and different absorption profiles.

Interestingly, we observed one patient with worsening of the PTA with repeated injections. This worsening may represent a dose-effect response, as postulated by Kopke et al. [7]; in this case, a higher than therapeutic dose might have damaged the inner ear. Based on this experience, we recommend starting with only one injection and to give another dose only in selected cases. Based on our data and on the experience of other Authors [2 6-8], we think that transtympanic steroids represent an effective option in the management of SSHL not responsive to traditional therapy.

Furthermore, it should be stressed that these results were obtained in patients usually considered beyond the possibility of treatment. Although a larger number of patients is necessary to confirm our protocol, we think, in accordance with other Authors [28], that transtympanic therapy can also be used as a first line therapy, especially in patients with severe to profound SSHL. The association of antioxidants is under investigation in order to improve our results.

Conclusions

Transtympanic steroid treatment represents an effective and safe solution in patients with SSHL in whom conventional treatment has failed. The optimal dosage, the type of steroids and the route of administration remain to be defined.

Acknowledgements

Authors are grateful to Mrs Diana Hearn for editing the manuscript.

References

1 Haberkamp TJ, Tanyeri HM. *Management of idiopathic sudden sensorineural hearing loss*. Am J Otol 1999;20:587-95.

2 Gianoli GJ, Li JC. *Transtympanic steroid for treatment of sudden hearing loss*. Otolaryngol Head Neck Surg 2001;125:142-6.

3 Rauch SD. *Intratympanic steroids for sensorineural hearing loss*. Otolaryngol Clin N Am 2004;37:1061-74.

4 Wilson WR, Byl FM, Laird N. *The efficacy of steroids in the treatment of idiopathic sudden hearing loss. A double-blind clinical study*. Arch Otolaryngol 1980;106:772-6.

5 Byl FM Jr. *Sudden hearing loss: eight years experience and suggested prognostic table*. Laryngoscope 1984;94:647-61.

6 Chandrasekhar SS. *Intratympanic dexamethasone for sudden sensorineural hearing loss: clinical and laboratory evaluation*. Otol Neurotol 2001;22:18-23.

7 Kopke RD, Hoffer ME, Wester D, O'Leary MJ, Jackson RL. *Targeted topical steroid therapy in sudden sensorineural hearing loss*. Otol Neurotol 2001;22:475-9.

8 Guan-Min H, Hung-Ching L, Min-Tsan S, Cheng-Chien Y, Hsun-Tien T. *Effectiveness of intratympanic dexamethasone injection in sudden-deafness patients as salvage treatment*. Laryngoscope 2004;114:1184-9.

9 Silverstein H, Choo D, Rosenberg SI, Kuhn J, Seidman M, Stein I. *Intratympanic steroid treatment of inner ear disease*

and tinnitus (Preliminary Report). ENT J 1996;75:468-76.

[10] Barrs DM, Keyser JS, Stallworth C, McElveen JT Jr. *Intratympanic steroid injections for intractable Ménière's disease*. Laryngoscope 2001;111:2100-4.

[11] Parnes LS, Sun AH, Freeman DJ. *Corticosteroid pharmacokinetics in the inner ear fluids: an animal study followed by clinical application*. Laryngoscope 1999;109(Suppl 91):1-17.

[12] Shimmer BP, Parker KL. *Adrenocorticotrophic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones*. In: Hardman JG, Limbird LE, Molinoff PB, Gilman AG, editors. *Goodman and Gilman's the pharmacological basis of the therapeutics.* 9th Edition. New York, NY: McGraw-Hill; 1996. p. 1459.

[13] Gross ND, Kempton JB, Trune DR. *Spironolactone blocks glucocorticoid-mediated hearing preservation in autoimmune mice*. Laryngoscope 2002;112:298-303.

[14] Seidman MD, Vivek P. *Intratympanic treatment of hearing loss with novel and traditional agents*. Otolaryngol Clin N Am 2004;37:973-90.

[15] Joachims HZ, Segal J, Golz A, Netzer A, Glodenberg D. *Antioxidants in treatment of idiopathic hearing loss*. Otol Neurotol 2003;24:572-5.

[16] Korver KD, Rybak LP, Whitworth C, Campbell KM. *Round window application of D-methionine provides complete cisplatin otoprotection*. Otolaryngol Head Neck Surg 2002;126:683-9.

[17] Gloddek B, Lamm K, Arnold W. *Pharmacological influence on inner ear endothelial cells in relation to the pathogenesis of sensorineural hearing loss*. Adv Otorhinolaryngol 2002;59:75-83.

[18] Lombardi D, Gaetani P, Marzatico F, Cafe C, Rodriguez y Baena R. *Effect of high dose methylprednisolone on antioxidant enzymes after experimental SAH*. J Neurol Sci 1992;111:13-9.

[19] Hall ED, Braughler JM, McCall JM. *Antioxidant effects in brain and spinal cord injury*. J Neurotrauma 1992;9(Suppl):S165-72.

[20] Liles WC, Dale DC, Klebanoff SJ. *Glucocorticoids inhibit apoptosis of human neutrophils*. Blood 1995;86:3181-8.

[21] Takumi Y, Nagelhus EA, Eidet J, Matsubara A, Usami S, Shinkawa H, et al. *Select types of supporting cell in the inner ear express aquaporin-4 water channel protein*. Eur J Neurosci 1998;10:3584-95.

[22] Mhatre AN, Steinbach S, Hribar K, Hoque AT, Lalwani AK. *Identification of aquaporin 5 (AQP5) within the cochlea: cDNA cloning and in situ localization*. Biochem Biophys Res Commun 1999;264:157-62.

[23] Fukushima M, Kitahara T, Uno Y, Fuse Y, Doi K, Kubo T. *Effects of intratympanic injection of steroid on changes in rat inner ear aquaporin expression*. Acta Otolaryngol 2002;122:600-6.

[24] Trune DR, Kempton JB. *Aldosterone and prednisolone control of cochlear function in MRL-MpJ-Fas autoimmune mice*. Hear Res 2001;155:9-20.

[25] Juhn SK, Rybak LP. *Labyrinthine barriers and cochlear homeostasis*. Acta Otolaryngol 1981;91:529-34.

[26] Banerjee A, Parnes LS. *The biology of intratympanic drug administration and pharmacodynamics of round window drug absorption*. Otolaryngol Clin N Am 2004;37:1035-51.

[27] Shirwany NA, Seidman MD, Tang W. *Effect of transtympanic injection of steroids on cochlear blood flow, auditory sensitivity, and histology in the Guinea Pig*. Am J Otol 1998;19:230-5.

[28] Light JP, Silverstein H. *Transtympanic perfusion: indications and limitations*. Curr Opin Otolaryngol Head Neck Surg 2004;12:378-83.

■ Received: February 8, 2005
Accepted: November 18, 2005

■ Address for correspondence: Dr. I. Dallan, U.O. ORL 2, Ospedale "Santa Chiara", via Savi 10, 56126 Pisa, Italy. Fax +39 050 993239. E mail: iacopodallan@tiscali.it